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(54) Stabilised interferon formulations and their preparation.

(57) Interferon formulations having in particular improved stability are in the form of a lyophilised pharmaceutical composition for reconstitution with sterile water, comprising interferon, an amino acid or derivative thereof selected from glycine, α-alanine and pharmaceutically acceptable salts thereof, and a compatible buffer system.

EP 0 082 481 A1

"STABILISED INTERFERON FORMULATIONS AND THEIR PREPARATION"

The present invention relates to interferon formulations having improved stability and to methods for their preparation.

The formulations of the present invention are useful in preparing sterile solutions, especially for injection or for use as nasal sprays, nasal solutions or ophthalmic solutions, or in the preparation of ointments, wherein interferon is the active drug. Interferon shows great potential in the treatment of a wide variety of disease states and particularly of various types of viral infections.

The well-known instability of interferon solutions makes it difficult to formulate stable compositions for clinical or veterinary use. Accordingly, it has been proposed to package interferon in lyophilised form for reconstitution with sterile water. Such a composition will contain a buffer to maintain a pharmaceutically acceptable pH when the solution is reconstituted and also sufficient sodium chloride to make the reconstituted solution isotonic. However, even in such a lyophilised composition, the interferon shows very limited and insufficient stability.

We have surprisingly discovered that the incorporation of certain amino acids and simple derivatives thereof into lyophilised interferon compositions yields a pharmaceutically

acceptable lyophilised product that has significantly improved stability. Furthermore, it is possible by this means to obtain further advantages such as greater ease in the lyophilisation step itself, better reconstitution of the lyophilised product, and better appearance of the product (in particular less colouration).

The present invention therefore provides a lyophilised pharmaceutical composition, for reconstitution with sterile water, comprising interferon together with a stabilising amount of an amino acid or derivative thereof selected from glycine, α-alanine and pharmaceutically acceptable salts thereof, and a compatible buffer system. Conveniently, there are about 1×10^4 to 5×10^8, preferably 1×10^6 to 1×10^8, International Units (I.U.) of interferon present for every 5 to 150 mgs. of amino acid or derivative thereof, the weight of any derivative of the amino acid being calculated as free amino acid.

The interferon used in the compositions according to the invention may be any interferon but is preferably a human interferon or another interferon suitable for use in humans, or a polypeptide exhibiting biological properties similar to those of such an interferon. In particular, the human interferon may be a leukocyte or a fibroblast interferon, and may have been prepared either by cultivation of leukocytes or fibroblasts or by cultivation of microorganisms suitably programmed, through genetic engineering, i.e. by recombinant DNA methods, to produce such interferons or equivalent polypeptides.

The human interferon may be α-interferon, β-interferon, or γ-interferon. It should be noted that a number of α-interferon species are known, usually designated by a numeral

after the Greek 1 tter. Also included within the scope of this invention are the so-called hybrid interferons wherein fragments of two or more native interferon species are joined. See, for example, EPA 51873 wherein hybrids of α-interferons are described. An example of such a hybrid α-interferon comprises the first 92 amino acids of α-1 interferon joined to a fragment comprising amino acids 92-165 of α-2 interferon (carboxy terminal portion). A particularly preferred form of α-interferon for use in the formulations of the present invention is α-2 interferon, especially α-2 interferon prepared by recombinant DNA methods, for example those disclosed by Nagata et al. in "Nature", Vol. 284, pages 316-320 (1980). Another preferred form of α-interferon for use in the formulations of the present invention is α-1 interferon, especially α-1 interferon prepared by recombinant DNA methods.

The specific activity of the α-2 interferon used in the formulations of the present invention should desirably be at least 5×10^7 I.U./mg. protein (of the interferon component), and preferably at least 1×10^8 I.U./mg. protein. Specific activity may be determined by measuring the antiviral activity as compared to the NIH reference standard and by measuring the total protein content using standard methods (e.g. the Lowry method). Similarly, high specific activity is desirable for clinical use of other interferons. At high levels of specific activity maintaining stability has hitherto been particularly difficult.

The amino acids are preferably used as the amino acids themselves, that is as glycine and α-alanine. Under these circumstances, about 5 to 150 mgs., preferably 5 to 25 mgs., especially 7 to 22 mgs., of α-alanine or especially of glycine will be present for 1×10^4 to 5×10^8 I.U. of interferon.

A composition containing these amounts of the ingredients is suitable for reconstitution by 1 ml. of sterile water.

The buffer system present in the compositions according to the invention is selected to be physiologically compatible and to maintain a desired pH in the reconstituted solution and also in the solution before lyophilisation. The pH of the reconstituted compositions of the present invention, especially those comprising α-2 interferon, should be about 6.5 to 8.0, preferably about 7.0 to 7.4. A preferred buffer system especially for compositions of α-2 interferon comprises disodium hydrogen phosphate and mono-sodium dihydrogen phosphate.

Whether an amino acid itself or a salt thereof is used, the buffer will be chosen to adjust the pH of the composition (after reconstitution) to a value within the desired range as indicated above.

Further components may be present in the compositions according to the invention, provided that they are physiologically compatible and are in no way detrimental to the interferon. In particular, a further stabiliser may be added. A preferred further stabiliser is albumin, especially human albumin when the compositions are designed for clinical use. For the above-mentioned quantity of amino acid (or derivative thereof calculated as amino acid), namely 5 to 150 mgs., (in particular preferably 5 to 25 mgs. of glycine), up to about 10 mg. of albumin, expecially about 1 mg., may be added.

If the amount of interferon (especially α-interferon) in a milliliter of reconstituted solution is to be less than about 5×10^6 I.U., the addition of albumin is very desir-

able.

A particularly preferred embodiment of the present invention contains the cited ingredients in the following proportions:

1×10^6 to 1×10^8 I. U. of α-interferon (especially α-2 interferon);
about 5 to 25 mgs., preferably 7 to 22 mgs., of α-alanine or especially of glycine;
a compatible buffer system designed to provide a pH of about 7.0 to 7.4 in the reconstituted solution;
and about 1 milligram of albumin.

The invention further provides a process for the preparation of a novel composition as defined above which comprises the steps of: dissolving the amino acid or derivative thereof selected from glycine, α-alanine and pharmaceutically acceptable salts thereof, a compatible buffer system, optionally human albumin, and the interferon in sterile water; and lyophilising the resulting solution.

The water used in reconstituting the compositions of the present invention may also contain compatible ingredients, in particular preservatives such as methyl or isopropyl p-hydroxy-benzoate. Such preservatives are advantageous where the resulting solutions will be used not as a single dose but for multiple applications, for example as nasal or ophthalmic solutions.

The following non-limiting examples illustrate the preparation of a sterile lyophilised powder for preparing injectable solutions of an interferon; the preferred interferon is α-2 interferon.

EXAMPLE 1

Solution for Lyophilisation (1000 vials; 1 ml. per vial)

Formula

Interferon	7.5×10^{10} I.U.
Disodium Hydrogen Phosphate, Anhydrous, USP, Reagent	2.27 grams per liter.
Sodium Dihydrogen Phosphate, USP	0.55 gram per liter.
Glycine, USP	20.0 grams per liter.
Human Albumin, USP	1.0 gram per liter.
Water for Injection, USP q.s. ad	1.0 liter.

Method of Manufacture

1. Charge a portion of the water into a suitable vessel equipped with an agitator.

2. Charge and dissolve with agitation the sodium phosphates.

3. Charge and dissolve with agitation the glycine.

4. Charge and dissolve with agitation the albumin.

5. Charge and dissolve with agitation the Interferon.

6. Bring the batch to final volume with Water for Injection, USP.

7. In a sterile area, aseptically filter the solution into a sterilised vessel through a sterilised 0.2 micron filter which has been washed and tested for integrity. Test the integrity of the filter after filtration.

8. Aseptically fill the solution into sterilised vials.

9. Aseptically load the filled vials into a sterilised lyophiliser.

10. Aseptically lyophilise the solution.

11. Aseptically stopper the vials.

12. Apply the seal and crimp the vials.

Method of Lyophilisation (Using a Shelf Lyophiliser)

1. Precool the shelves to -30°C.

2. Load the vials into the chamber.

3. Allow the solutions to freeze. Cool the condenser to -45°C. or below. Start the vacuum. Maintain shelf temperature at -30°C. for at least 12 hours.

4. Increase shelf temperatures at a relatively constant rate to no more than +25°C. in a period of no less than about 24 hours.

5. When the product temperature reaches +25°C., flood the chamber with sterile nitrogen until it reaches atmospheric pressure. Stopper the vials in the chambers.

6. Remove the vials from the chamber and seal them.

EXAMPLE 2

A preferred formulation of the present invention wherein the interferon is α-2 interferon is prepared by following the procedure of Example 1, using α-2 interferon as the interferon but substituting α-alanine for glycine.

EXAMPLE 3

A preferred formulation of the present invention wherein the interferon is α-1 interferon is prepared by following the procedure of Example 1 but using α-1 interferon as the interferon.

EXAMPLE 4

Another preferred formulation of the present invention is prepared by following the procedure of Example 1 but using α-1 interferon as the interferon and substituting α-alanine for glycine.

Per cent recovery of α-2 Interferon from different formulations under different storage conditions.

Storage time (months)	Storage Temperature (°C.)	*Formulations I	II	III
Initial		100	100	100
		% recovery of α-2 Interferon		
1	25	-	-	83
3	4	89	67	-
3	25	83	-	23
6	4	106	52	-
6	25	106	-	-
6	35	115	-	-

*Formulations:

I: According to present invention, lyophilised;

II: Phosphate buffer with saline, pH 7.4, solution;

III: Formulation II, lyophilised.

CLAIMS

1. A lyophilised pharmaceutical composition for reconstitution with sterile water, comprising interferon, a stabilising amount of an amino acid or derivative thereof selected from glycine, α-alanine and pharmaceutically acceptable salts thereof, and a compatible buffer system.

2. A composition as claimed in claim 1 wherein there are about 1×10^4 to 5×10^8 International Units of interferon present for every 5 to 150 mgs. of amino acid or derivative thereof, the weight of any derivative of the amino acid being calculated as the free amino acid.

3. A composition as claimed in claim 1 or claim 2 comprising also up to about 10 mgs., preferably about 1 mg., of human albumin for every 5 to 150 mgs. of amino acid or pharmaceutically acceptable salt thereof.

4. A composition as claimed in any of claims 1 to 3 wherein the buffer system is designed to maintain a pH of about 6.5 to 8.0, preferably about 7.0 to 7.4, after reconstitution.

5. A composition as claimed in any of claims 1 to 4 wherein the buffer system comprises disodium hydrogen phosphate and monosodium dihydrogen phosphate.

6. A composition as claimed in any of claims 1 to 5 wherein the interferon is a human interferon, preferably a leukocyte interferon or a fibroblast interferon, in particular where the interferon is α-interferon or β-interferon, especially α-2 interferon or α-1 interferon.

7. A composition claimed in any of claims 1 to 6 wherein

the interferon has been prepared by recombinant DNA methods.

8. A composition as claimed in any of claims 1 to 7 wherein there are 5 to 25 mgs., preferably 7 to 22 mgs., of glycine for every 1×10^4 to 5×10^8 International Units of interferon.

9. A composition as claimed in any of claims 1 to 7 containing 1×10^6 to 1×10^8 International Units of interferon for every 5 to 150 mgs., preferably 5 to 25 mgs., especially 7 to 22 mgs., of α-alanine, glycine or pharmaceutically acceptable salts thereof, the weight of any derivative of the glycine or α-alanine being calculated as free amino acid.

10. A composition as claimed in any of claims 1 to 9 comprising: 1×10^6 to 1×10^8 International Units of α-interferon, especially α-2 interferon;
about 5 to 25 mgs., preferably 7 to 22 mgs., of α-alanine or especially glycine;
a compatible buffer system, especially a mixture of disodium hydrogen phosphate and monosodium dihydrogen phosphate, designed to provide a pH of about 1.0 to 7.4 in the reconstituted solution;
and about 1 mg. of human albumin.

11. A process for the preparation of a composition as claimed in claim 1 which comprises the steps of: dissolving the amino acid or derivative thereof selected from glycine, α-alanine and pharmaceutically acceptable salts thereof, a compatible buffer system, optionally human albumin, and the interferon, in sterile water; and lyophilising the resulting solution.

12. A method for the stabilisation of a lyophilised pharmaceutical composition for reconstitution with sterile water, comprising interferon and a compatible buffer system, which comprises incorporating a stabilising amount of an amino acid or derivative thereof selected from glycine, α-alanine and pharmaceutically acceptable salts thereof into the composition before lyophilisation.

European Patent Office

EUROPEAN SEARCH REPORT

0082481
Application number

EP 82 11 1665

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. ³)
P,X	FR-A-2 505 657 (INSTITUT PASTEUR) *Pages 17-18; claims 1-9*	1-12	A 61 K 45/02
A	EP-A-0 027 573 (THE MEDICAL COLLEGE OF WISCONSIN, INC.) *Pag 5, line 11 - page 6, line 20*	1-12	
A	BIOLOGICAL ABSTRACTS, vol. 68, no. 8, 1979, no. 49094, Philadelphia, Pa., (USA); A.S.LEVINE: "Initial clinical trials in cancer patients of polyriboinosinic-polyribocytidylic acid stabilized with poly-L-lysine, in carboxymethylcellulose (poly(ICLC), a highly effective interferon inducer". & CANCER-RES. 39(5), 1645-50, 1979. *Abstract*	1-12	

TECHNICAL FIELDS SEARCHED (Int. Cl. ³)

A 61 K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	21-03-1983	BRINKMANN C.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
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T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
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BIOLOGICAL ABSTRACTS, vol. 68, no. 8, 1979, no. 49099, Philadelphia, Pa., (USA); A.S.Levine

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Description

The present invention relates to interferon formulations having improved stability and to methods for their preparation.

The formulations of the present invention are useful in preparing sterile solutions, especially for injection or for use as nasal sprays, nasal solutions or ophthalmic solutions, or in the preparation of ointments, wherein interferon is the active drug. Interferon shows great potential in the treatment of a wide variety of disease states and particularly of various types of viral infections.

The well-known instability of interferon solutions makes it difficult to formulate stable compositions for clinical or veterinary use. Accordingly, it has been proposed to package interferon in lyophilised form for reconstitution with sterile water. Such a composition will contain a buffer to maintain a pharmaceutically acceptable pH when the solution is reconstituted and also sufficient sodium chloride to make the reconstituted solution isotonic. However, even in such a lyophilised composition, the interferon shows very limited and insufficient stability.

We have surprisingly discovered that the incorporation of certain amino acids and simple derivatives thereof into lyophilised interferon compositions yields a pharmaceutically acceptable lyophilised product that has significantly improved stability. Furthermore, it is possible by this means to obtain further advantages such as greater ease in the lyophilisation step itself, better reconstitution of the lyophilised product, and better appearance of the product (in particular less colouration).

The present invention therefore provides a lyophilised pharmaceutical composition, for reconstitution with sterile water, comprising interferon together with a stabilising amount of an amino acid or derivative thereof selected from glycine, α-alanine and pharmaceutically acceptable salts thereof, and a compatible buffer system. Conveniently, there are about 1×10^4 to 5×10^8, preferably 1×10^6 to 1×10^8, International Units (I.U.) of interferon present for every 5 to 150 mg of amino acid or derivative thereof, the weight of any derivative of the amino acid being calculated as free amino acid.

The interferon used in the compositions according to the invention may be any interferon but is preferably a human interferon or another interferon suitable for use in humans, or a polypeptide exhibiting biological properties similar to those of such an interferon. In particular, the human interferon may be a leukocyte or a fibroblast interferon, and may have been prepared either by cultivation of leukocytes or fibroblasts or by cultivation of microorganisms suitably programmed, through genetic engineering, i.e. by recombinant DNA methods, to produce such interferons or equivalent polypeptides.

The human interferon may be α-interferon, β-interferon, or γ-interferon. It should be noted that a number of α-interferon species are known, usually designated by a numeral after the Greek letter. Also included within the scope of this invention are the so-called hybrid interferons wherein fragments of two or more native interferon species are joined. See, for example, EPA 51873 wherein hybrids of α-interferons are described. An example of such a hybrid α-interferon comprises the first 92 amino acids of α-1 interferon joined to a fragment comprising amino acids 92—165 of α-2 interferon (carboxy terminal portion). A particularly preferred form of α-interferon for use in the formulations of the present invention is α-2 interferon, especially α-2 interferon prepared by recombinant DNA methods, for example those disclosed by Nagata et al. in "Nature", Vol. 284, pages 316—320 (1980). Another preferred form of α-interferon for use in the formulations of the present invention is α-1 interferon, especially α-1 interferon prepared by recombinant DNA methods.

The specific activity of the α-2 interferon used in the formulations of the present invention should desirably be at least 5×10^7 I.U./mg. protein (of the interferon component), and preferably at least 1×10^8 I.U./mg. protein. Specific activity may be determined by measuring the antiviral activity as compared to the NIH reference standard and by measuring the total protein content using standard methods (e.g. the Lowry method). Similarly, high specific activity is desirable for clinical use of other interferons. At high levels of specific activity maintaining stability has hitherto been particularly difficult.

The amino acids are preferably used as the amino acids themselves, that is as glycine and α-alanine. Under these circumstances, about 5 to 150 mgs., preferably 5 to 25 mg, especially 7 to 22 mg, of α-alanine or especially of glycine will be present for 1×10^4 to 5×10^8 I.U. of interferon.

A composition containing these amounts of the ingredients is suitable for reconstitution by 1 ml. of sterile water.

The buffer system present in the compositions according to the invention is selected to be physiologically compatible and to maintain a desired pH in the reconstituted solution and also in the solution before lyophilisation. The pH of the reconstituted compositions of the present invention, especially those comprising α-2 interferon, should be about 6.5 to 8.0, preferably about 7.0 to 7.4. A preferred buffer system especially for compositions of α-2 interferon comprises disodium hydrogen phosphate and mono-sodium dihydrogen phosphate.

Whether an amino acid itself or a salt thereof is used, the buffer will be chosen to adjust the pH of the composition (after reconstitution) to a value within the desired range as indicated above.

Further components may be present in the compositions according to the invention, provided that they are physiologically compatible and are in no way detrimental to the interferon. In particular, a further stabiliser may be added. A preferred further stabiliser is albumin, especially human albumin when the compositions are designed for clinical use. For the above-mentioned quantity of amino acid

(or derivative ther of calculated as amino acid), nam ly 5 to 150 mg, (in particular preferably 5 to 25 mgs. of glycine), up to about 10 mg. of albumin, specially about 1 mg., may b added.

If the amount f interferon (especially α-interferon) in a milliliter of reconstituted solution is to be less than about 5×10^6 I.U., th addition of albumin is very desirable.

A particularly preferred embodiment of the present invention contains the cited ingredients in the following proportions:

1×10^6 to 1×10^8 I.U. of α-interferon (especially α-2 interferon);

about 5 to 25 mg, preferably 7 to 22 mg, of α-alanine or especially of glycine;

a compatible buffer system designed to provide a pH of about 7.0 to 7.4 in the reconstituted solution;

and about 1 milligram of albumin.

The invention further provides a process for the preparation of a novel composition as defined above which comprises the steps of: dissolving the amino acid or derivative thereof selected from glycine, α-alanine and pharmaceutically acceptable salts thereof, a compatible buffer system, optionally human albumin, and the interferon in sterile water; and lyophilising the resulting solution.

The water used in reconstituting the compositions of the present invention may also contain compatible ingredients, in particular preservatives such as methyl or isopropyl p-hydroxy-benzoate. Such preservatives are advantageous where the resulting solutions will be used not as a single dose but for multiple applications, for example as nasal or ophthalmic solutions.

The following non-limiting examples illustrate the preparation of a sterile lyophilised powder for preparing injectable solutions of an interferon; the preferred interferon is α-2 interferon.

Example 1

Solution for Lyophilisation (1000 vials; 1 ml. per vial)

Formula	
Interferon	7.5×10^{10} I.U.
Disodium Hydrogen Phosphate, Anhydrous, USP, Reagent	2.27 grams per liter.
Sodium Dihydrogen Phosphate, USP	0.55 gram per liter.
Glycine, USP	20.0 grams per liter.
Human Albumin, USP	1.0 gram per liter.
Water for Injection, USP q.s. ad	1.0 liter.

Method of manufacture

1. Charge a portion of the water into a suitable vessel equipped with an agitator.
2. Charge and dissolve with agitation the sodium phosphates.
3. Charge and dissolve with agitation the glycine.
4. Charge and dissolve with agitation the albumin.
5. Charge and dissolve with agitation the Interferon.
6. Bring the batch to final volume with Water for Injection, USP.
7. In a sterile area, aseptically filter the solution into a sterilised vessel through a sterilised 0.2 micron filter which has been washed and tested for integrity. Test the integrity of the filter after filtration.
8. Aseptically fill the solution into sterilised vials.
9. Aseptically load the filled vials into a sterilised lyophiliser.
10. Aseptically lyophilise the solution.
11. Aseptically stopper the vials.
12. Apply the seal and crimp the vials.

Method of lyophilisation (using a shelf lyophiliser)

1. Precool the shelves to −30°C.
2. Load the vials into the chamber.
3. Allow the solutions to freeze. Cool the condenser to −45°C. or below. Start the vacuum. Maintain shelf temperature at −30°C. for at least 12 hours.
4. Incr ase sh lf temperatures at a relatively constant rat to no mor than +25°C. in a period of no less than about 24 hours.
5. When the product temp ratur reaches +25°C., flood the chamber with sterile nitrogen until it reaches atmosph ric pressure. Stopper the vials in th chamb rs.
6. Remove the vials from th chamber and seal them.

Example 2

A preferred formulation of the present invention wherein the interferon is α-2 interf ron is pr pared by following the procedure of Example 1, using α-2 int rferon as the interferon but substituting α-alanine for glycine.

Example 3

A preferred formulation of the present invention wherein the interferon is α-1 interferon is prepared by following the procedure of Example 1 but using α-1 interferon as the interferon.

Example 4

Another preferred formulation of the present invention is prepared by following the procedure of Example 1 but using α-1 interferon as the interferon and substituting α-alanine for glycine.

Per cent recovery of α-2 Interferon from different formulations under different storage conditions.

Storage time (months)	Storage temperature (°C.)	*Formulations I	II	III
Initial		100	100	100
		% recovery of α-2 Interferon		
1	25	—	—	83
3	4	89	67	—
3	25	83	—	23
6	4	106	52	—
6	25	106	—	—
6	35	115	—	—

*Formulations:
I: According to present invention, lyophilised;
II: Phosphate buffer with saline, pH 7.4, solution;
III: Formulation II, lyophilised.

Claims

1. A ~~lyophilised pharmaceutical composition~~ for reconstitution with sterile water, comprising interferon, a stabilising amount of an amino acid or derivative thereof selected from glycine, α-alanine and pharmaceutically acceptable salts thereof, and a compatible buffer system.

2. A composition as claimed in claim 1 wherein there are about 1×10^4 to 5×10^8 International Units of interferon present for every 5 to 150 mg of amino acid or derivative thereof, the weight of any derivative of the amino acid being calculated as the free amino acid.

3. A composition as claimed in claim 1 or claim 2 comprising also up to about 10 mg, preferably about 1 mg., of human albumin for every 5 to 150 mg of amino acid or pharmaceutically acceptable salt thereof.

4. A composition as claimed in any of claims 1 to 3 wherein the buffer system is designed to maintain a pH of about 6.5 to 8.0, preferably about 7.0 to 7.4, after reconstitution.

5. A composition as claimed in any of claims 1 to 4 wherein the buffer system comprises disodium hydrogen phosphate and monosodium dihydrogen phosphate.

6. A composition as claimed in any of claims 1 to 5 wherein the interferon is a human interferon, preferably a leukocyte interferon or a fibroblast interferon, in particular where the interferon is α-interferon or β-interferon, especially α-2 interferon or α-1 interferon.

7. A composition claimed in any of claims 1 to 6 wherein the interferon has been prepared by r combinant DNA methods.

8. A composition as claimed in any of claims 1 to 7 wherein there are 5 to 25 mg, preferably 7 to 22 mg, of glycine for every 1×10^4 to 5×10^8 International Units of interferon.

9. A composition as claimed in any of claims 1 to 7 containing 1×10^6 to 1×10^8 International Units of interferon for every 5 to 150 mg, preferably 5 to 25 mg, specially 7 to 22 mg, of α-alanine, glycine or pharmaceutically acceptable salts thereof, the weight of any derivative of the glycine or α-alanine being calculated as free amino acid.

10. A composition as claimed in any of claims 1 to 9 comprising: 1×10^6 to 1×10^8 International Units of α-interferon, especially α-2 interferon;

about 5 to 25 mg, preferably 7 to 22 mg, of α-alanine or especially glycine;

a compatibl buff r system, especially a mixtur of disodium hydrogen phosphate and monosodium dihydrogen phosphate, designed to provide a pH of about 7.0 to 7.4 in the reconstituted solution;

and about 1 mg. of human albumin.

11. A process for the preparation of a composition as claimed in claim 1 which comprises the steps of: dissolving the amino acid or derivative thereof selected from glycine, α-alanine and pharmaceutically acceptable salts thereof, a compatible buffer system, optionally human albumin, and the interferon, in sterile water; and lyophilising the resulting solution.

12. A method for the stabilisation of a lyophilised pharmaceutical composition for reconstitution with sterile water, comprising interferon and a compatible buffer system, which comprises incorporating a stabilising amount of an amino acid or derivative thereof selected from glycine, α-alanine and pharmaceutically acceptable salts thereof into the composition before lyophilisation.

Revendications

1. Composition pharmaceutique lyophilisée pour reconstitution avec de l'eau stérile, comprenant l'interféron, une quantité stabilisante d'un acide aminé ou sel de celui-ci choisi parmi glycine, α-alanine et leurs sels acceptables en pharmacie, et un système tampon compatible.

2. Composition selon la revendication 1 caractérisée en ce qu'elle comprend environ 1×10^4 à 5×10^8 Unités internationales l'interféron pour chaque 5 à 150 mg d'acide aminé ou dérivé de celui-ci, le poids de tout dérivé d'acide aminé étant calculé par rapport de l'acide aminé libre.

3. Composition selon la revendication 1 ou 2 caractérisée en ce qu'elle comprend également jusqu'à environ 10 mg, et de préférence environ 1 mg d'albumine humaine pour chaque 5 à 150 mg d'acide aminé ou sel acceptable en pharmacie de celui-ci.

4. Composition selon l'une des revendications 1 à 3 caractérisée en ce que le système tampon est destiné à maintenir un pH d'environ 6,5 à 8 et de préférence environ 7 à 7,4 après reconstitution.

5. Composition selon l'une des revendications 1 à 4 caractérisée en ce que le système tampon comprend de l'hydrogéno phosphate disodique et du dihydrogéno phosphate monosodique.

6. Composition selon l'une des revendications 1 à 5 caractérisé en ce que l'interféron est un interféron humain, de préférence un interféron de leucocyte ou un interféron de fibroblaset, en particulier ou l'interféron est α-interféron ou β-interféron, spécialement 1'α-2 interféron ou α-1 interféron.

7. Composition selon l'une des revendications 1 à 6 caractérisée en ce que l'interféron a été préparé par des procédés de recombinaison d'ADN.

8. Composition selon l'une des revendications 1 à 7, caractérisée en ce qu'elle comprend 5 à 25 mg, de préférence 7 à 22 mg de glycine pour chaque 1×10^4 à 5×10^8 Unités Internationales d'interféron.

9. Composition selon l'une des revendications 1 à 7 caractérisée en ce qu'elle comprend 1×10^6 à 1×10^8 Unités internationales d'interféron pour chaque 5 à 150 mg, de préférence 5 à 25 mg, et spécialement 7 à 22 mg de α-alanine, glycine ou de leurs sels acceptables en pharmacie, le poids de tout dérivé de glycine ou α-alanine étant calculé par rapport à l'acide aminé.

10. Composition selon l'une des revendications 1 à 9, caractérisée en ce qu'elle comprend 1×10^6 à 1×10^8 Unités internationals d'interféron, et spécialement α-2 interféron; environ 5 à 25 mg, et de préférence 7 à 22 mg d'α-alanine ou en particulier glycine; Un système tampon compatible, en particulier un mélange d'hydrogéno phosphate disodique et de di-hydrogéno phosphate monosodique, destiné à fournir un pH d'environ 7 à 7,4 dans la solution reconstituée, et environ 1 mg d'albumin humaine.

11. Procédé de préparation d'une composition selon la revendication 1 caractérisé en ce qu'il comprend les étapes de: dissoudre l'acide aminé ou dérivé de celui-ci choisi parmi glycine, α-alanine et sels acceptables en pharmacie de ceux-ci, un système tampon compatible, éventuellement de l'albumine humaine, et l'interféron, dans de l'eau stérile; et lyophiliser la solution résultante.

12. Procédé pour la stabilisation d'une composition pharmaceutique lyophilisée pour reconstitution avec de l'eau stérile, comprenant l'interféron et un système tampon compatible, caractérisé en ce qu'il comprend l'incorporation d'une quantité stabilisante d'un acide aminé ou dérivé de celui-ci choisi parmi glycine, α-alanine et sels acceptables en pharmacie de ceux-ci dans la composition avant lyophilisation.

Pat ntansprüche

1. Lyophilisi rte pharmazeutische Zusammensetzung zur Rekonstitution mit sterilem Wasser, enthaltend Interferon, eine stabilisierende Menge einer Aminosäure ausgewählt aus Glycin, α-Alanin und deren pharmazeutisch unbedenklichen Salzen oder eines Derivats derselben sowie ein verträgliches Puff r-System.

2. Zusammensetzung nach Anspruch 1, dadurch gekennz ichnet, daß etwa 1×10^4 bis 5×10^8 Internationale Einheiten Interferon auf jeweils 5 bis 150 mg der Aminosäure oder ihres Derivats vorliegen, wobei das Gewicht irgendeines Derivats der Aminosäure als frei Aminosäure berechnet wird.

3. Zusammensetzung nach Anspruch 1 oder Anspruch 2, dadurch gekennzeichnet, daß sie außerdem bis zu etwa 10 mg, vorzugsweise etwa 1 mg, Humanalbumin auf jeweils 5 bis 150 mg der Aminosäure oder ihres pharmazeutisch unbedenklichen Salzes enthält.

4. Zusammensetzung nach irgendeinem der Ansprüche 1 bis 3, dadurch gekennzeichnet, daß das Puffer-System so eingerichtet ist, daß es einen pH von etwa 6,5 bis 8,0, vorzugsweise etwa 7,0 bis 7,4, nach der Rekonstitution aufrechterhält.

5. Zusammensetzung nach irgendeinem der Ansprüche 1 bis 4, dadurch gekennzeichnet, daß das Puffer-System Dinatriumhydrogenphosphat und Mononatriumdihydrogenphosphat enthält.

6. Zusammensetzung nach irgendeinem der Ansprüche 1 bis 5, dadurch gekennzeichnet, daß das Interferon ein Human-Interferon, vorzugsweise ein Leukozyten-Interferon oder ein Fibroblasten-Interferon ist, insbesondere dann, wenn das Interferon α-Interferon oder β-Interferon, speziell α-2-Interferon oder α-1-Interferon, ist.

7. Zusammensetzung nach irgendeinem der Ansprüche 1 bis 6, dadurch gekennzeichnet, daß das Interferon durch DNA-Rekombinationsmethoden hergestellt ist.

8. Zusammensetzung nach irgendeinem der Ansprüche 1 bis 7, dadurch gekennzeichnet, daß 5 bis 25 mg, vorzugsweise 7 bis 22 mg, Glycin auf jeweils 1×10^4 bis 5×10^8 Internationale Einheiten Interferon vorliegen.

9. Zusammensetzung nach irgendeinem der Ansprüche 1 bis 7, dadurch gekennzeichnet, daß sie 1×10^6 bis 1×10^8 Internationale Einheiten Interferon auf jeweils 5 bis 150 mg, vorzugsweise 5 bis 25 mg, insbesondere 7 bis 22 mg, α-Alanin, Glycin oder deren pharmazeutisch unbedenklicher Salze enthält, wobei das Gewicht irgendeines Derivats des Glycins oder α-Alanins als freie Aminosäure berechnet wird.

10. Zusammensetzung nach irgendeinem der Ansprüche 1 bis 9, dadurch gekennzeichnet, daß sie 1×10^6 bis 1×10^8 Internationale Einheiten α-Interferon, insbesondere α-2-Interferon, etwa 5 bis 25 mg, vorzugsweise 7 bis 22 mg, α-Alanin oder insbesondere Glycin, ein verträgliches Puffer-System, das so eingerichtet ist, daß es einen pH von etwa 7,0 bis 7,4 in der rekonstituierten Lösung herstellt, insbesondere eine Mischung aus Dinatriumhydrogenphosphat und Monoatriumdihydrogenphosphat, sowie etwa 1 mg Human-Albumin enthält.

11. Verfahren zur Herstellung einer Zusammensetzung nach Anspruch 1 mit den Schritten: Auflösen der Aminosäure ausgewählt aus Glycin, α-Alanin und deren pharmazeutisch unbedenklichen Salzen oder eines Derivats derselben, eines verträgliches Puffer-Systems, gegebenenfalls des Human-Albumins, und des Interferons in sterilem Wasser und Lyophilisieren der erhaltenen Lösung.

12. Verfahren zur Stabilisierung einer lyophilisierten pharmazeutischen Zusammensetzung zur Rekonstitution mit sterilem Wasser, enthaltend Interferon und ein verträgliches Puffer-System, dadurch gekennzeichnet, daß eine stabilisierende Menge einer Aminosäure ausgewählt aus Glycin, α-Alanin und deren pharmazeutisch unbedenklichen Salzen oder eines Derivats derselben vor dem Lyophilisieren in die Zusammensetzung eingearbeitet wird.

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Description

The present invention relates to α-interferon formulations having improved stability and to methods for their preparation.

The formulations of the present invention are useful in preparing sterile solutions, especially for injection or for use as nasal sprays, nasal solutions or ophthalmic solutions, or in the preparation of ointments, wherein α-interferon is the active drug. α-Interferon shows great potential in the treatment of a wide variety of disease states and particularly of various types of viral infections.

The well-known instability of α-interferon solutions makes it difficult to formulate stable compositions for clinical or veterinary use. Accordingly, it has been proposed to package α-interferon in lyophilised form for reconstitution with sterile water. Such a composition will contain a buffer to maintain a pharmaceutically acceptable pH when the solution is reconstituted and also sufficient sodium chloride to make the reconstituted solution isotonic. However, even in such a lyophilised composition, the α-interferon shows very limited and insufficient stability.

We have surprisingly discovered that the incorporation of certain amino acids and simple derivatives thereof into lyophilised α-interferon compositions yields a pharmaceutically acceptable lyophilised product that has significantly improved stability. Furthermore, it is possible by this means to obtain further advantages such as greater ease in the lyophilisation step itself, better reconstitution of the lyophilised product and better appearance of the product (in particular less colouration).

The present invention therefore provides a lyophilised pharmaceutical composition, for reconstitution with sterile water, comprising α-interferon together with a stabilising amount of an amino acid or derivative thereof selected from glycine, α-alanine and pharmaceutically acceptable salts thereof, and a compatibl buffer system designed to maintain a pH of about 6.5 to 8.0 after reconstitution. Conveniently, there are about 1×10^4 to 5×10^8, preferably 1×10^6 to 1×10^8, International Units (I.U.) of α-interferon present for every 5 to 150 mg of amino acid or derivative thereof, the weight of any derivative of the amino acid being calculated as free amino acid.

The α-interferon used in the compositions according to the invention is preferably a human α-interferon or another α-interferon suitable for use in humans, or a polypeptide exhibiting biological properties similar to those of such an α-interferon. In particular, the human α-interferon may be a leukocyte interferon, and may have been prepared either by cultivation of leukocytes or by cultivation of microorganisms suitably programmed, through genetic engineering, i.e. by recombinant DNA methods, to produce such α-interferons or equivalent polypeptides.

It should be noted that a number of α-interferon species are known, usually designated by a numeral after the Greek letter. Also included within the scope of this invention are the so-called hybrid interferons wherein fragments of two or more native interferon species are joined. See, for example, EPA 51873 wherein hybrids of α-interferons are described. An example of such a hybrid α-interferon comprises the first 92 amino acids of α-1 interferon joined to a fragment comprising amino acids 92—165 of α-2 interferon (carboxy terminal portion). A particularly preferred form of α-interferon for use in the formulations of the present invention is α-2 interferon, especially α-2 interferon prepared by recombinant DNA methods, for example those disclosed by Nagata et al, in "Nature", Vol. 284, pages 316—320 (1980). Another preferred form of α-interferon for use in the formulations of the present invention is α-1 interferon, especially α-1 interferon prepared by recombinant DNA methods.

The specific activity of the α-2 interferon used in the formulations of the present invention should desirably be at least 5×10^7 I.U./mg. protein (of the interferon component), and preferably at least 1×10^8 I.U./mg. protein. Specific activity may be determined by measuring the antiviral activity as compared to the NIH reference standard and by measuring the total protein content using standard methods (e.g. the Lowry method). Similarly, high specific activity is desirable for clinical use of other interferons. At high levels of specific activity maintaining stability has hitherto been particularly difficult.

The amino acids are preferably used as the amino acids themselves, that is a glycine and α-alanine. Under these circumstances, about 5 to 150 mgs., preferably 5 to 25 mg, especially 7 to 22 mg, of α-alanine or especially of glycine will be present for 1×10^4 to 5×10^8 I.U. of interferon.

A composition containing these amounts of the ingredients is suitable for reconstitution by 1 ml. of sterile water.

The buffer system present in the compositions according to the invention is selected to be physiologically compatible and to maintain a desired pH in the reconstituted solution and also in the solution before lyophilisation. The pH of the reconstituted compositions of the present invention, especially those comprising α-2 interferon, should be about 6.5 to 8.0, preferably about 7.0 to 7.4. A preferred buffer system especially for compositions of α-2 interferon comprises disodium hydrogen phosphate and monosodium dihydrogen phosphate.

Whether an amino acid itself or a salt thereof is used, the buffer will be chosen to adjust the pH of the composition (after reconsitution) to a value within the desired range as indicated above.

Further components may be present in the compositions according to the invention, provided that they are physiologically compatible and are in no way detrimental to the interferon. In particular, a further stabiliser may be added. A preferred further stabiliser is albumin, especially human albumin when the compositions are designed for clinical use. For the above-mentioned quantity of amino acid (or derivative

thereof calculated as amino acid), namely 5 to 150 mg, (in particular preferably 5 to 25 mgs. of glycine), up to about 10 mg. of albumin, especially about 1 mg, may be added.

If the amount of α-interferon in a mililiter of reconstituted solution is to be less than about 5×10^6 I.U., the addition of albumin is very desirable.

A particularly preferred embodiment of the present invention contains the cited ingredients in the f llowing proportions.

1×10^6 to 1×10^8 of α-interferon (especially α-2 interferon);

about 5 to 25 mg, preferably 7 to 22 mg, of α-alanine or especially of glycine;

a compatible buffer system designed to provide a pH of about 7.0 to 7.4 in the reconstituted solution;

and about 1 miligram of albumin.

The invention further provides a process for the preparation of a novel composition as defined above which comprises the steps of: dissolving the amino acid or derivative thereof selected from glycine, α-alanine and pharmaceutically acceptable salts thereof, a compatible buffer system, optionally human albumin, and the interferon in sterile water; and lyophilising the resulting solution.

The water used in reconstituting the compositions of the present invention may also contain compatible ingredients, in particular preservatives such as methyl or isopropyl *p*-hydroxy-benzoate. Such preservatives are advantageous where the resulting solutions will be used not as a single dose but for multiple applications, for example as nasal or ophthalmic solutions.

The following non-limiting examples illustrate the preparation of a sterile lyophilised powder for preparing injectable solutions of an interferon; the preferred interferon is α-2 interferon.

Example 1

Solution for Lyophilisation (1000 vials; 1 ml. per vial)

Formula	
Interferon	7.5×10^{10} I.U.
Disodium Hydrogen Phosphate, Anhydrous, USP, Reagent	2,27 grams per liter.
Sodium Dihydrogen Phosphate, USP	0.55 gram per liter.
Glycine, USP	20.0 grams per liter.
Human Albumin, USP	1.0 gram per liter.
Water for Injection, USP q.s. ad	1.0 liter.

Method of manufacture:

1. Charge a portion of the water into a suitable vessel equipped with an agitator.
2. Charge and dissolve with agitation the sodium phosphates.
3. Charge and dissolve with agitation the glycine.
4. Charge and dissolve with agitation the albumin.
5. Charge and dissolve with agitation the Interferon.
6. Bring the batch to final volume with Water for Injection, USP.
7. In a sterile area, aseptically filter the solution into a sterilized vessel through a sterilised 0.2 micron filter which has been washed and tested for integrity. Test the integrity of the filter after filtration.
8. Aseptically fill the solution into sterilised vials.
9. Aseptically load the filled vials into a sterilised lyophiliser.
10. Aseptically lyophilise the solution.
11. Aseptically stopper the vials.
12. Apply the seal and crimp the vials.

Method of lyophilisation (using a shelf lyophiliser)

1. Precool the shelves to −30°C.
2. Load the vials into the chamber.
3. Allow th solutions to freeze. Cool the condenser to −45°C or below. Start the vacuum. Maintain shelf temperature at −30°C for at least 12 hours.
4. Increase shelf temperatures at a relatively constant rate to no more than +25°C in a period of no less than about 24 hours.
5. When the product temperature reaches +25°C, flood the chamber with sterile nitrogen until it reaches atmospheric pressure. Stopper th vials in the chambers.
6. Remove the vials from the chamber and seal them.

Example 2

A preferred formulation of the present invention wherein th interferon is α-2 interferon is prepar d by following the procedure f Exampl 1, using α-2 interferon as the interf ron but substituting α-interferon for glycine.

Example 3

A preferred formulation of the present invention wherein the interferon is α-1 interferon is prepared by following the procedure of Example 1 but using α-1 interferon as the interferon.

Example 4

Another preferred formulation of the present invention is prepared by following the procedure of Example 1 but using α-1 interferon as the interferon and substituting α-alanine for glycine.

Per cent recovery of α-2 Interferon from different formulations under different storage conditions.

Storage time (months)	Storage temperature (°C)	*Formulations I	II	III
Initial		100	100	100
		% recovery of α-2 Interferon		
1	25	—	—	83
3	4	89	67	—
3	25	83	—	23
6	4	106	52	—
6	25	106	—	—
6	35	115	—	—

*Formulations:
I: According to present invention, lyophilised;
II: Phosphate buffer with saline, pH 7,4, solution
III: Formulation II, lyophilised.

Claims

1. A lyophilised pharmaceutical composition for reconstitution with sterile water, comprising α-interferon, a stabilising amount of an amino acid or derivative thereof selected from glycine, α-alanine and pharmaceutically acceptable salts thereof, and a compatible buffer system designed to maintain a pH of about 6.5 to 8.0 after reconstitution.

2. A composition as claimed in claim 1 wherein there are about 1×10^4 to 5×10^8 International Units of α-interferon present for every 5 to 150 mg of amino acid or derivative thereof, the weight of any derivative of the amino acid being calculated as the free amino acid.

3. A composition as claimed in claim 1 or claim 2 comprising also up to about 10 mg, preferably about 1 mg, of human albumin for every 5 to 150 mg of amino acid or pharmaceutically acceptable salt thereof.

4. A composition as claimed in any of the claims 1 to 3 wherein the buffer system is designed to maintain a pH of about 7.0 to 7.4 after reconstitution.

5. A composition as claimed in any of the claims 1 to 4 wherein the buffer system comprises disodium hydrogen phosphate and monosodium dihydrogen phosphate.

6. A composition as claimed in any of the claims 1 to 5 wherein the α-interferon is a human interferon, preferably α-2 interferon or α-1 interferon.

7. A composition as claimed in any of claims 1 to 6 wherein the α-interferon has been prepared by recombinant DNA methods.

8. A composition as claimed in any of claims 1 to 7 wherein there are by 5 to 25 mg, preferably 7 to 22 mg, of glycine for every 1×10^4 to 5×10^8 International Units of α-interferon.

9. A composition as claimed in any of claims 1 to 7 containing 1×10^6 to 1×10^8 International Units of α-interferon for every 5 to 150 mg, preferably 5 to 25 mg, especially 7 to 22 mg, of α-interferon, glycine or pharmaceutically acceptable salts thereof, the weight of any derivative of the glycine or α-interferon being calculated as fr e amino acid.

10. A composition as claimed in any of claims 1 to 9 comprising: 1×10^6 to 1×10^8 International Units of α-interferon, especially α-2 interferon;

about 5 to 25 mg, preferably 7 to 22 mg, of α-alanine or especially glycine;

a compatible buffer system, especially a mixture of disodium hydrogen phosphate and monosodium dihydrogen phosphate, designed to provide a pH of bout 7.0 to 7.4 in reconstituted solution;

and about 1 mg of human albumin.

11. A process for the preparation of a composition as claimed in claim 1 which comprises the steps of: dissolving the amino acid or a derivative thereof selected from glycine, α-alanine and pharmaceutically acceptable salts thereof, a compatible buffer system designed to provide a pH of about 6.5 to 8.0 in the reconstituted solution, optionally human albumin, and the α-interferon, in sterile water; and lyophilising the resulting solution.

12. A method for stabilising of a lyophilised pharmaceutical composition for reconstitution with sterile water to a pH of about 6.5 to 8.0 after reconstitution, comprising α-interferon and a compatible, suitabl buffer system, which comprises incorporating a stabilising amount of an amino acid or derivative thereof selected from glycine, α-alanine and pharmaceutically acceptable salts thereof into the composition before lyophilisation.

Patentansprüche

1. Lyophilisierte pharmazeutische Zusammensetzung zur Rekonstitution mit sterilem Wasser, enthaltend α-Interferon, eine stabilisierende Menge einer Aminosäure oder eines Derivats derselben ausgewählt aus Glycin, α-Alanin und deren pharmazeutisch unbedenklichen Salzen sowie ein verträgliches Puffersystem, um einen pH von etwa 6,5 bis 8,0 nach Rekonstitution aufrecht zu erhalten.

2. Zusammensetzung nach Anspruch 1, dadurch gekennzeichnet, daß etwa 1×10^4 bis 5×10^8 Internationale Einheiten α-Interferon auf jeweils 5 bis 150 mg der Aminosäure oder ihres Derivats vorliegen, wobei das Gewicht irgendeines Derivats der Aminosäure als freie Aminosäure berechnet wird.

3. Zusammensetzung nach Anspruch 1 oder Anspruch 2, dadurch gekennzeichnet, daß sie außerdem bis zu etwa 10 mg, vorzugsweise etwa 1 mg, Humanalbumin auf jeweils 5 bis 150 mg der Aminosäure oder ihres pharmazeutisch unbedenklichen Salzes enthält.

4. Zusammensetzung nach irgendeinem der Ansprüche 1 bis 3, dadurch gekennzeichnet, daß das Puffer-System so eingerichtet ist, daß es einen pH von etwa 7,0 bis 7,4, nach der Rekonstitution aufrechterhählt.

5. Zusammensetzung nach irgendeinem der Ansprüche 1 bis 4, dadurch gekennzeichnet, daß das Puffer-System Dinatriumhydrogenphosphat und Mononatriumhydrogenphosphat enthält.

6. Zusammensetzung nach irgendeinem der Ansprüche 1 bis 5, dadurch gekennzeichnet, daß das α-Interferon ein Human-Interferon vorzugsweise α-2-Interferon oder α-1-Interferon, ist.

7. Zusammensetzung nach irgendeinem der Ansprüche 1 bis 6, dadurch gekennzeichnet, daß das α-Interferon durch DNA-Rekombinationsmethoden hergestellt ist.

8. Zusammensetzung nach irgendeinem der Ansprüche 1 bis 7, dadurch gekennzeichnet, daß 5 bis 25 mg, vorzugsweise 7 bis 22 mg, Glycin auf jeweils 1×10^4 bis 5×10^8 Internationale Einheiten α-Interferon vorliegen.

9. Zusammensetzung nach irgendeinem der Ansprüche 1 bis 7, dadurch gekennzeichnet, daß sie 1×10^5 bis 1×10^8 Internationale Einheiten α-Interferon auf jeweils 5 bis 150 mg, vorzugsweise 5 bis 25 mg, insbesondere 7 bis 22 mg, α-Alanin, Glycin oder deren pharmazeutisch unbedenklicher Salze enthält, wobei das Gewicht irgendeines Derivats des Glycins oder α-Alanins als freie Aminosäure berechnet wird.

10. Zusammensetzung nach irgendeinem der Ansprüche 1 bis 9, dadurch gekennzeichnet, daß sie 1×10^6 bis 1×10^8 Internationale Einheiten α-Interferon, insbesondere α-2-Interferon, etwa 5 bis 25 mg, vorzugsweise 7 bis 22 mg, α-Alanin oder insbesondere Glycin, ein verträgliches Puffer-System, insbesondere eine Mischung aus Dinatriumhydrogenphosphat und Mononatriumhydrogenphosphat, zur Herstellung eines pH von etwa 7 bis 7,4 in der rekonstituierten Lösung sowie etwa 1 mg Human-Albumin enthält.

11. Verfahren zur Herstellung einer Zusammensetzung nach Anspruch 1 mit den Schritten: Auflösen der Aminosäure oder eines Derivats derselben ausgewählt aus Glycin, α-Alanin und deren pharmazeutisch unbedenklichen Salzen, eines verträglichen Puffer-Systems zur Herstellung eines pH von etwa 6,5 bis 8,0 in der rekonstituierten Lösung, gegebenenfalls des Human-Albumins, und des α-Interferons in sterilem Wasser und Lyophilisieren der erhaltenen Lösung.

12. Verfahren zur Stabilisierung einer lyophilisierten pharmazeutischen Zusammensetzung zur Rekonstitution mit sterilem Wasser auf einen pH von etwa 6,5 bis 8,0 nach Rekonstitution, enthaltend α-Interferon und ein verträgliches geeignetes Puffer-System, dadurch gekennzeichnet, daß eine stabilisierende Menge einer Aminosäure oder eines Derivats derselben ausgewählt aus Glycin, α-Alanin und der n pharmazeutisch unb denklichen Salzen vor d m Lyophilisi ren in die Zusammensetzung eingearbeitet wird.

Revendications

1. Composition pharmaceutique lyophilisée pour reconstitution avec de l'eau stérile, comprenant l'α-interféron, un quantité stabilisante d'un acide aminé ou sel de celui-ci choisi parmi glycine, α-alanine et

leurs s ls acc ptabl s en pharmacie, et une systéme tampon compatible, conçu pour maintenir un pH d'environ 6,5 à 8,0 après reconstitution.

2. Composition selon la revendication 1 caractérisée en c qu'elle comprend environ 1×10^4 à 5×10^8 Unités Internationales d'α-interféron pour chaque 5 à 150 mg d'acide aminé ou dériv´ de celui-ci, le poids de tout dérivé d'acide aminé étant calculé par rapport à l'acide amin´ libre.

3. Composition selon la revendication 1 ou 2 caractérisée en ce qu'elle comprend également jusqu'à environ 10 mg, et de préférence 1 mg d'albumine humaine pour chaque 5 à 150 mg d'acide aminé ou sel acceptable en pharmacie de celui-ci.

4. Composition selon l'une des revendications 1 à 3, caractérisée en ce que le système tampon est destiné à maintenir un pH d'environ 7,0 à 7,4 après reconstitution.

5. Composition selon l'une des revendications 1 à 4, caractérisée en ce que le système tampon comprend de l'hydrogéno phosphate disodique et du dihydrogéno phosphate monosodique.

6. Composition selon l'une des revendications 1 à 5, caractérisée en ce que l'α-interféron est un interféron humain, de préférence α-2 interféron ou α-1 interféron.

7. Composition selon l'une des revendications 1 à 6, caractérisée en ce que l'α-interféron a été préparé par des procédés de recombinaison d'ADN.

8. Composition selon l'une des revendications 1 à 7, caractérisée en ce qu'elle comprend 5 à 25 mg, de préférence 7 à 22 mg, de glycine pour chaque 1×10^4 à 5×10^8 Unités Internationales d'α-interféron.

9. Composition selon l'une des revendications 1 à 7, caractérisée en ce qu'elle comprend 1×10^6 à 1×10^8 Unités Internationales d'α-interféron pour chaque 5 à 150 mg , de préférence 5 à 25 mg, et spécialement 7 à 22 mg d'α-alanine, glycine ou de leurs sels acceptables en pharmacie, le poids de tout dérivé de glycine ou α-alanine étant calculé par rapport à l'acide aminé libre.

10. Composition selon l'une des revendications 1 à 9, caractérisée en ce qu'elle comprend 1×10^6 à 1×10^8 Unités Internationales d'α-interféron, et spécialement α-2 interféron; environ 5 à 25 mg, et de préférence 7 à 22 mg d'α-alanine ou en particulier de glycine; un système tampon compatible, en particulier un mélange d'hydrogéno phosphate disodique et de dihydrogéno phosphate monosidique, destiné à fournir un pH d'environ 7,0 à 7,4 dans la solution reconstituée, et environ 1 mg d'albumine humaine.

11. Procédé de préparation d'une composition selon la revendication 1 caractérisé en ce qu'il comprend les étapes de: dissoudre l'acide aminé ou dérivé de celui-ci choisi parmi glycine, α-alanine et sels acceptables en pharmacie de ceux-ci, un système tampon compatible, conçu pour produire un pH d'environ 6,5 à 8,0 dans la solution reconstituée, éventuellement de l'albumine humaine, et l'α-interféron, dans de l'eau stérile; et lyophiliser la solution résultante.

12. Procédé pour la stabilisation d'une composition pharmaceutique lyophilisée pour reconstitution avec de l'eau stérile à une pH d'environ 6,5 à 8,0 après reconstitution, comprenant l'α-interféron et un système tampon compatible et approprié, caractérisé en ce qu'il comprend l'incorporation d'une quantité stabilisante d'un acide aminé ou dérivé de celui-ci choisi parmi glycine, α-alanine et sels acceptables en pharmacie de ceux-ci dans la composition avant lyophilisation.